第21章

Introduction to the pharmacology of CNS Drugs

- 中樞神經作用藥物均作用於specific receptors
- 研究 CNS phsiology ，可由 convulsion , long-term memory 探討其機轉(agonist, antagonist)
- 由已知臨床效用 闡明CNS藥理機轉
- Ion channels and neurotransmitter receptors
- 神經細胞有二種channels
  - 1. Voltage gate :sodium, calcium ,potassium channel
  - 2. Ligand gate channel (ionotropic receptor)藉神經傳導物質與channel 結合而打開。

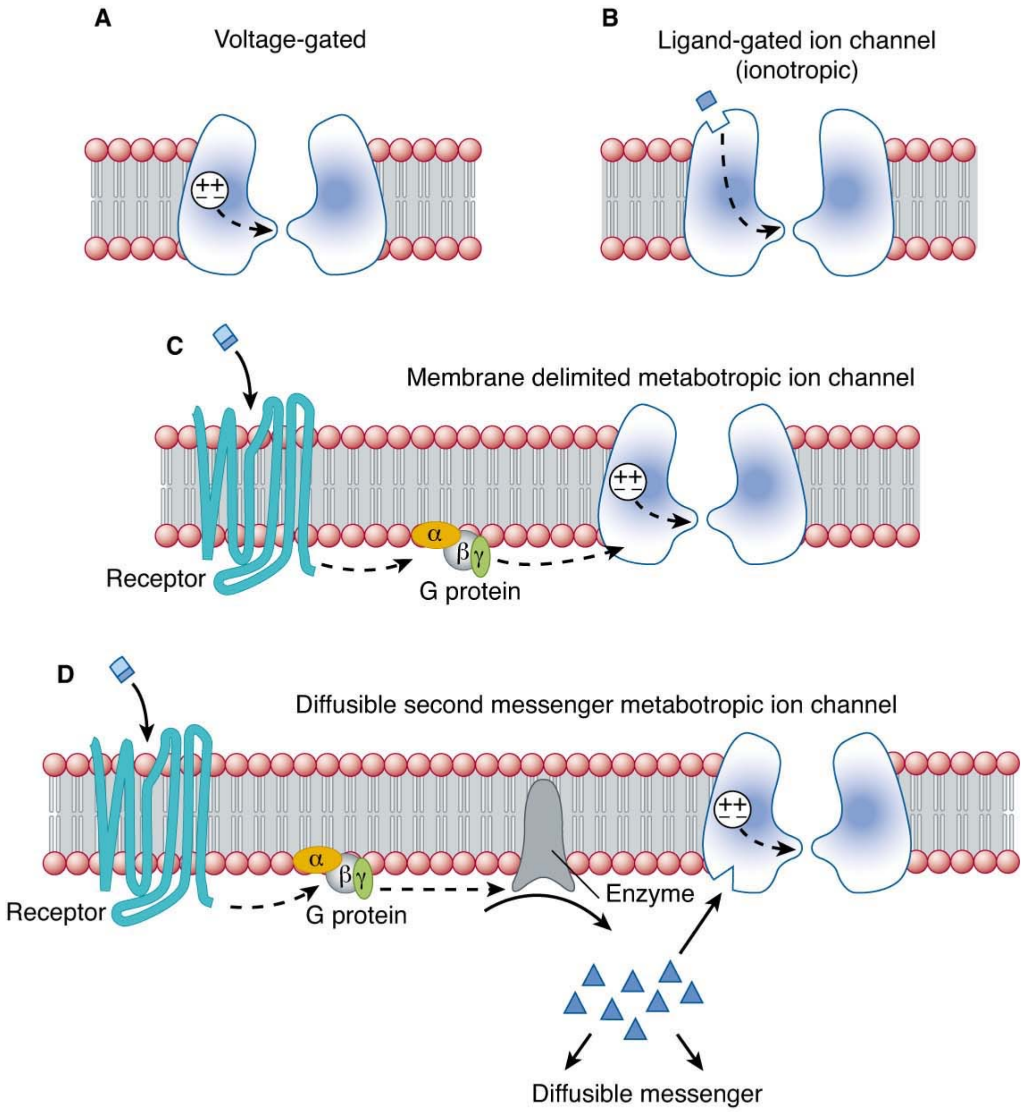

FIGURE 21–2 Types of ion channels and neurotransmitter receptors in the CNS. **A** shows a voltage-gated channel in which a voltage sensor component of the protein controls the gating (*broken arrow*) of the channel. **B** shows a ligand-gated channel in which the binding of the neurotransmitter to the ionotropic channel receptor controls the gating (*broken arrow*) of the channel. **C** shows a G protein-coupled (metabotropic) receptor, which, when bound, activates a G protein that then interacts directly to modulate an ion channel. **D** shows a G protein-coupled receptor, which, when bound, activates a G protein that then activates an enzyme. The activated enzyme generates a diffusible second messenger, eg, cAMP, which interacts to modulate an ion channel.

Sites of drug action

1. Presynaptic region

- 藥物作用於神經傳達物質之synthesis, storage, metabolism 及 release 。藉由抑制其合成或儲存 →作用位置
- Reserpine: depletes monoamine synapse of transmitter (干擾細胞內storage)
- Amphetamine: release catecholamines (adrenergic synapses)
- Capsaicin: release peptide substance P (sensory neuron)
- Tetanus toxin: block the release of transmitters
- Cocaine: block the uptake of CA (adrenergic synapses)
- Acetylcholine: 由酵素分解→ inactivation (非reuptake)
- Anticholinesterase: block Ach degradtion → 延長Ach作用

Sites of drug action

2. Postsynaptic region:

- Strychnine : block glycine receptor → convulsant action
- Barbiturate : block excitatory ionotropic receptor
- 高劑量 methylxanthine : block cAMP metabolism →延長突觸後作用

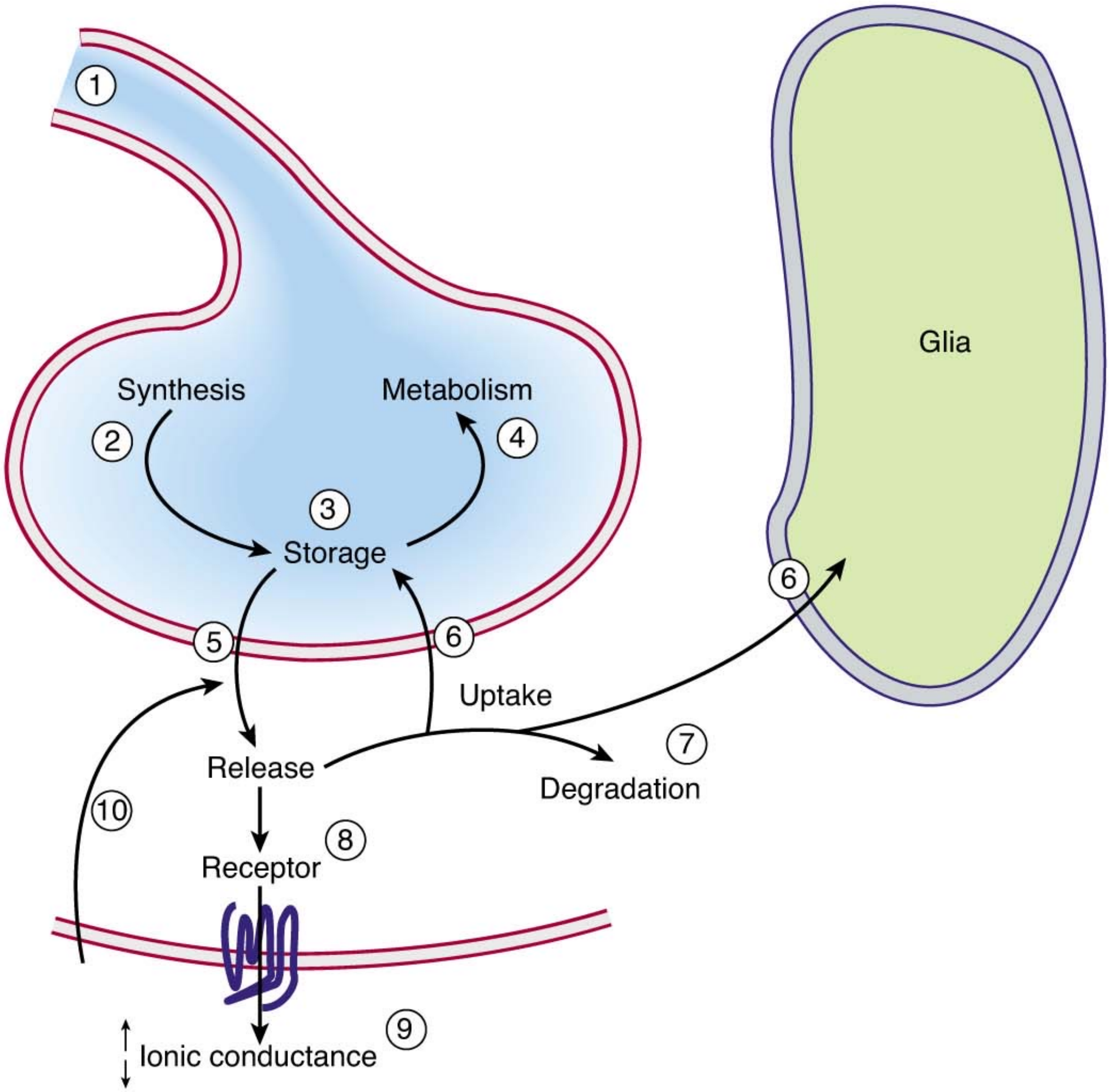

FIGURE 21–5 Sites of drug action. Schematic drawing of steps at which drugs can alter synaptic transmission. (1) Action potential in presynaptic fiber; (2) synthesis of transmitter; (3) storage; (4) metabolism; (5) release; (6) reuptake into the nerve ending or uptake into a glial cell; (7) degradation; (8) receptor for the transmitter; (9) receptor-induced increase or decrease in ionic conductance; (10) retrograde signaling.

Cellular organization of the brain

1. Hierarchical systems (階層系統)

- 直接於感官知覺及 motor control 功能的神經路徑。
- Picrotoxin: selectively blocking $GABA_A$ receptor → convulsion

p363 Fig. 21-6

2. Nonspecific of diffuse neuronal systems

(非特異性或擴散性神經系統)

- 神經系統之monoamines-norepinephrine, dopamine,

  5-hydroxytryptamine (5-HT, serotonin) 均屬此類

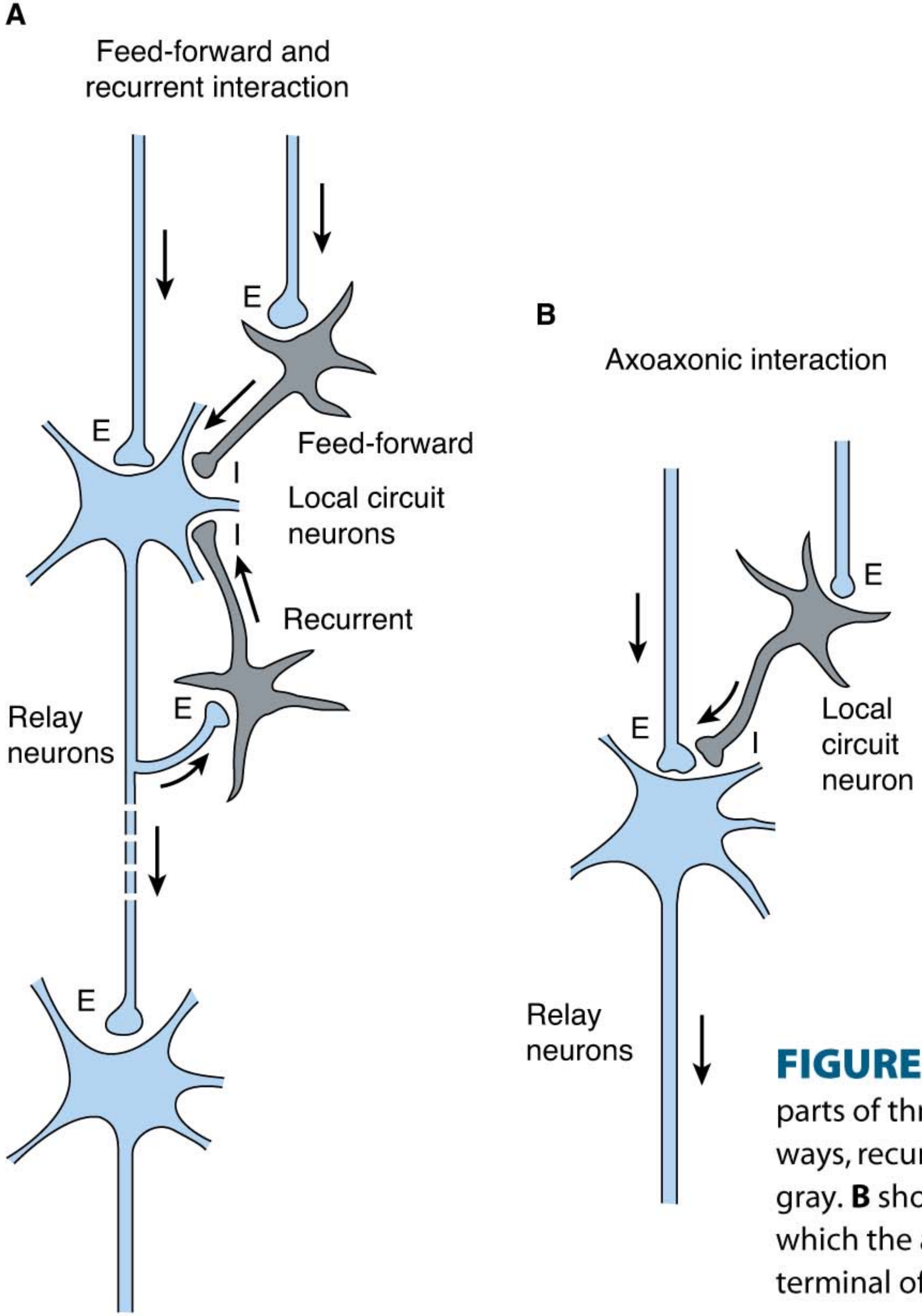

FIGURE 21–6 Pathways in the central nervous system. **A** shows parts of three relay neurons (blue) and two types of inhibitory pathways, recurrent and feed-forward. The inhibitory neurons are shown in gray. **B** shows the pathway responsible for presynaptic inhibition in which the axon of an inhibitory neuron (gray) synapses on the axon terminal of an excitatory fiber (blue).

Central neurotransmitters

一、Amino Acids:

A. Glutamate

B. GABA and Glycine

二、Acetylcholine

三、Biogenic monoamines

(1) Catecholamines

A. dopamine

B. Norepinephrine

(2) 5-hydroxytryptamine (serotonin)

四、Peptides

五、Nitric oxide

六、Endocannabinoids

Central neurotransmitters (1)

一、Amino acids

1. Acidic amino acids (Glutamate)

Excitatory synaptic transmission is mediated by glutamate.

→Glutamate release →cleft (Ca^{++}-dependent exocytosis)

→作用在postsynaptic glutamate receptor:

AMPAR: α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor

NMDA: N-methyl-D-aspartate receptor

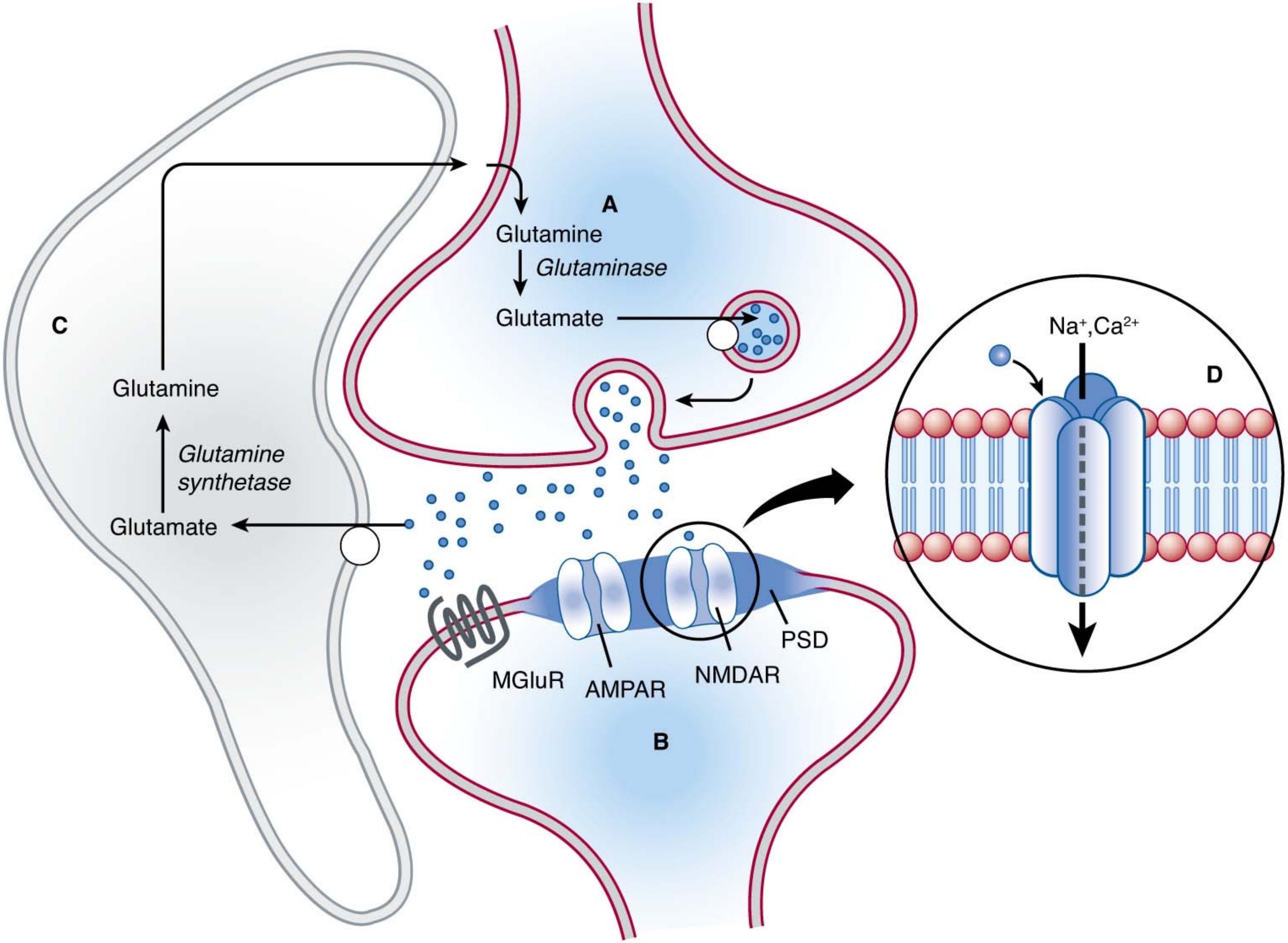

FIGURE 21–7 Schematic diagram of a glutamate synapse. Glutamine is imported into the glutamatergic neuron **(A)** and converted into glutamate by glutaminase. The glutamate is then concentrated in vesicles by the vesicular glutamate transporter. Upon release into the synapse, glutamate can interact with AMPA and NMDA ionotropic receptor channels (AMPAR, NMDAR) in the postsynaptic density (PSD) and with metabotropic receptors (MGluR) on the postsynaptic cell **(B)**. Synaptic transmission is terminated by active transport of the glutamate into a neighboring glial cell **(C)** by a glutamate transporter. It is synthesized into glutamine by glutamine synthetase and exported into the glutamatergic axon. **(D)** shows a model NMDA receptor channel complex consisting of a tetrameric protein that becomes permeable to Na^+ and Ca^{2+} when it binds a glutamate molecule.

Central neurotransmitters (2)

2. Neutral amino acid (GABA, Glycine)
   - Inhibitory neurotransmitters
   - 存在於brain及spinal cord
     - →$GABA_A$: Diazepam (打開 chloride ion channel)
     - →$GABA_B$: Baclofen anti-spastic drug (coupled to G protein, 抑制Ca^{++} channel, 活化 K^+ channel)
   - 又抑制adenylyl cyclase → cAMP generation↓

二、Acetylcholine

- Ach 存在於中樞neostriatum (新紋狀體)
  - Medial septal nucleus (內側中隔神經核)
  - Reticular formation (網狀組織)
- 與cognitive function (memory) 有關
- Alzheimer Disease (Presenile dementia年輕型)
  - 因cholinergic neuron ↓

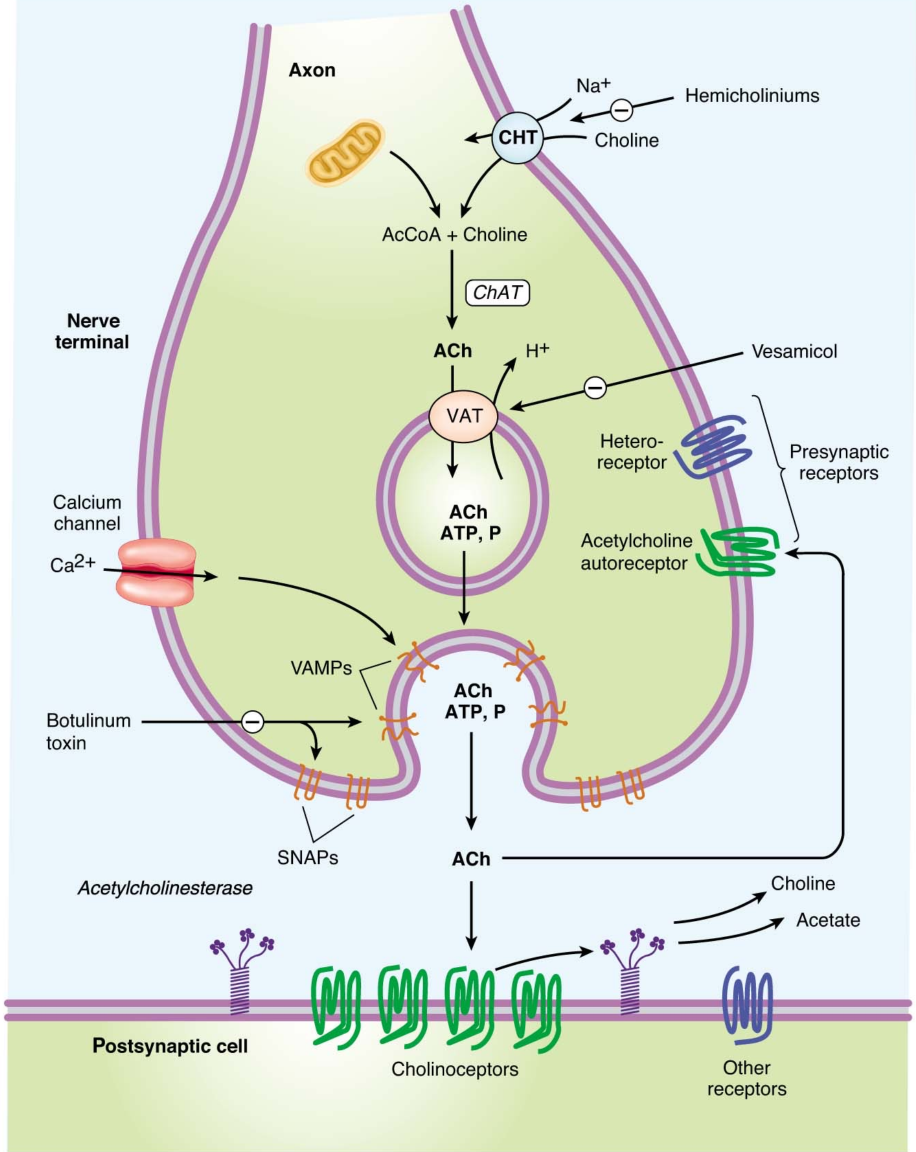

FIGURE 6–3 Schematic illustration of a generalized cholinergic junction (not to scale). Choline is transported into the presynaptic nerve terminal by a sodium-dependent choline transporter (CHT). This transporter can be inhibited by hemicholinium drugs. In the cytoplasm, acetylcholine is synthesized from choline and acetyl Co-A (AcCoA) by the enzyme choline acetyltransferase (ChAT). Acetylcholine is then transported into the storage vesicle by a second carrier, the vesicle-associated transporter (VAT), which can be inhibited by vesamicol. Peptides (P), adenosine triphosphate (ATP), and proteoglycan are also stored in the vesicle. Release of transmitter occurs when voltage-sensitive calcium channels in the terminal membrane are opened, allowing an influx of calcium. The resulting increase in intracellular calcium causes fusion of vesicles with the surface membrane and exocytotic expulsion of acetylcholine and cotransmitters into the junctional cleft (see text). This step can be blocked by botulinum toxin. Acetylcholine's action is terminated by metabolism by the enzyme acetylcholinesterase. Receptors on the presynaptic nerve ending modulate transmitter release. SNAPs, synaptosome-associated proteins; VAMPs, vesicle-associated membrane proteins.

三、Biogenic monoamines

1. Dopamine

– DA路徑即

→連結黑質(substantia nigra)和新紋狀體(neostriatum)

→projection linking 腹側頂蓋核(ventral tegmental region)→再傳到邊緣系統(limbic system)

- 尤其limbic cortex 路徑與 antiparkinsonism drug(levodopa)有關
- Tubero basal ventral hypothalamus對於 hypothalmohypophysial function扮演重要角色
- D_1-like (D_1, D_5)
- D_2-like (D_2, D_3, D_4)

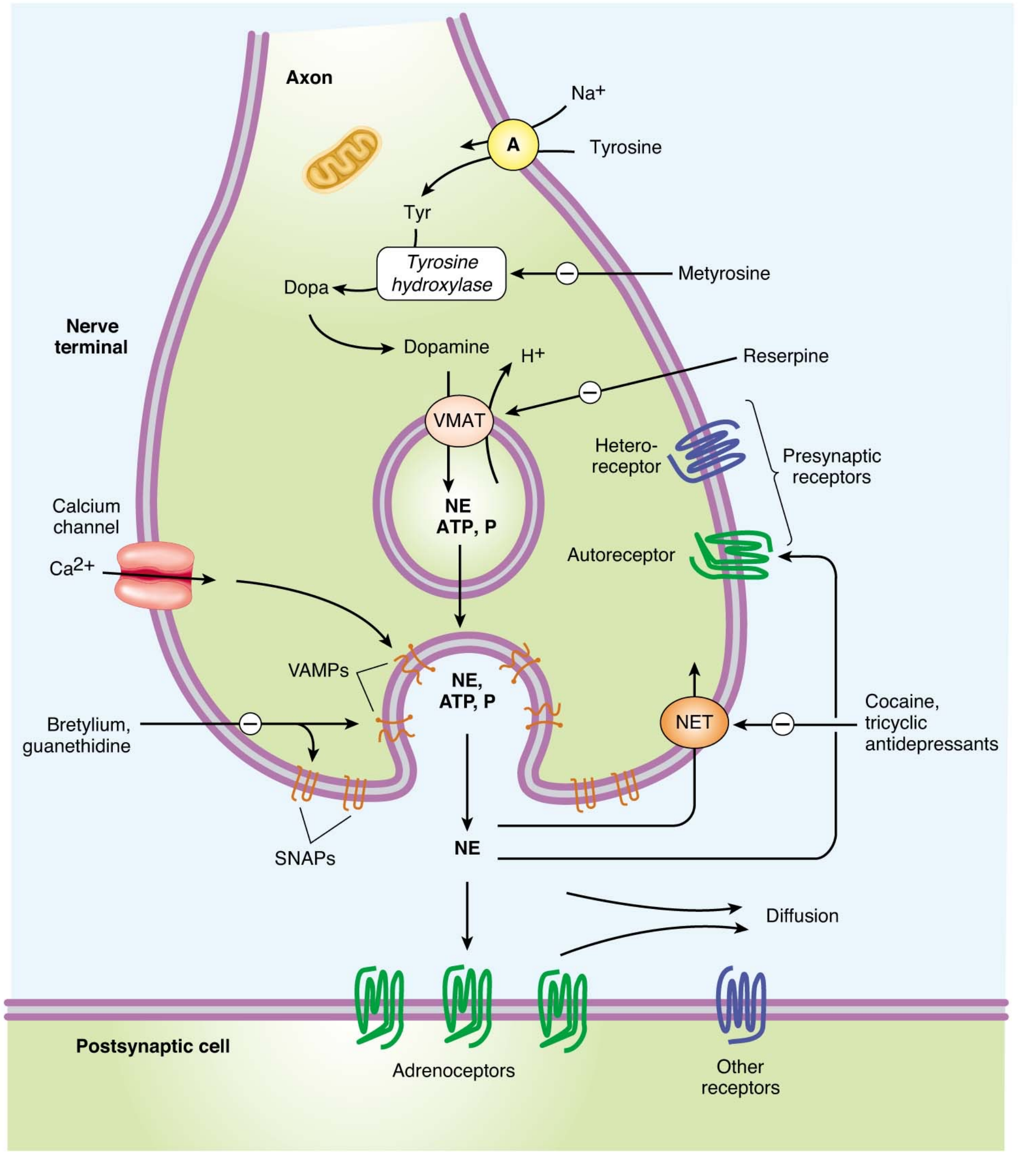

FIGURE 6–4 Schematic diagram of a generalized noradrenergic junction (not to scale). Tyrosine is transported into the noradrenergic ending or varicosity by a sodium-dependent carrier (A). Tyrosine is converted to dopamine (see Figure 6–5 for details), and transported into the vesicle by the vesicular monoamine transporter (VMAT), which can be blocked by reserpine. The same carrier transports norepinephrine (NE) and several other amines into these granules. Dopamine is converted to NE in the vesicle by dopamine-β-hydroxylase. Physiologic release of transmitter occurs when an action potential opens voltage-sensitive calcium channels and increases intracellular calcium. Fusion of vesicles with the surface membrane results in expulsion of norepinephrine, cotransmitters, and dopamine-β-hydroxylase. Release can be blocked by drugs such as guanethidine and bretylium. After release, norepinephrine diffuses out of the cleft or is transported into the cytoplasm of the terminal by the norepinephrine transporter (NET), which can be blocked by cocaine and tricyclic antidepressants, or into postjunctional or perijunctional cells. Regulatory receptors are present on the presynaptic terminal. SNAPs, synaptosome-associated proteins; VAMPs, vesicle-associated membrane proteins.

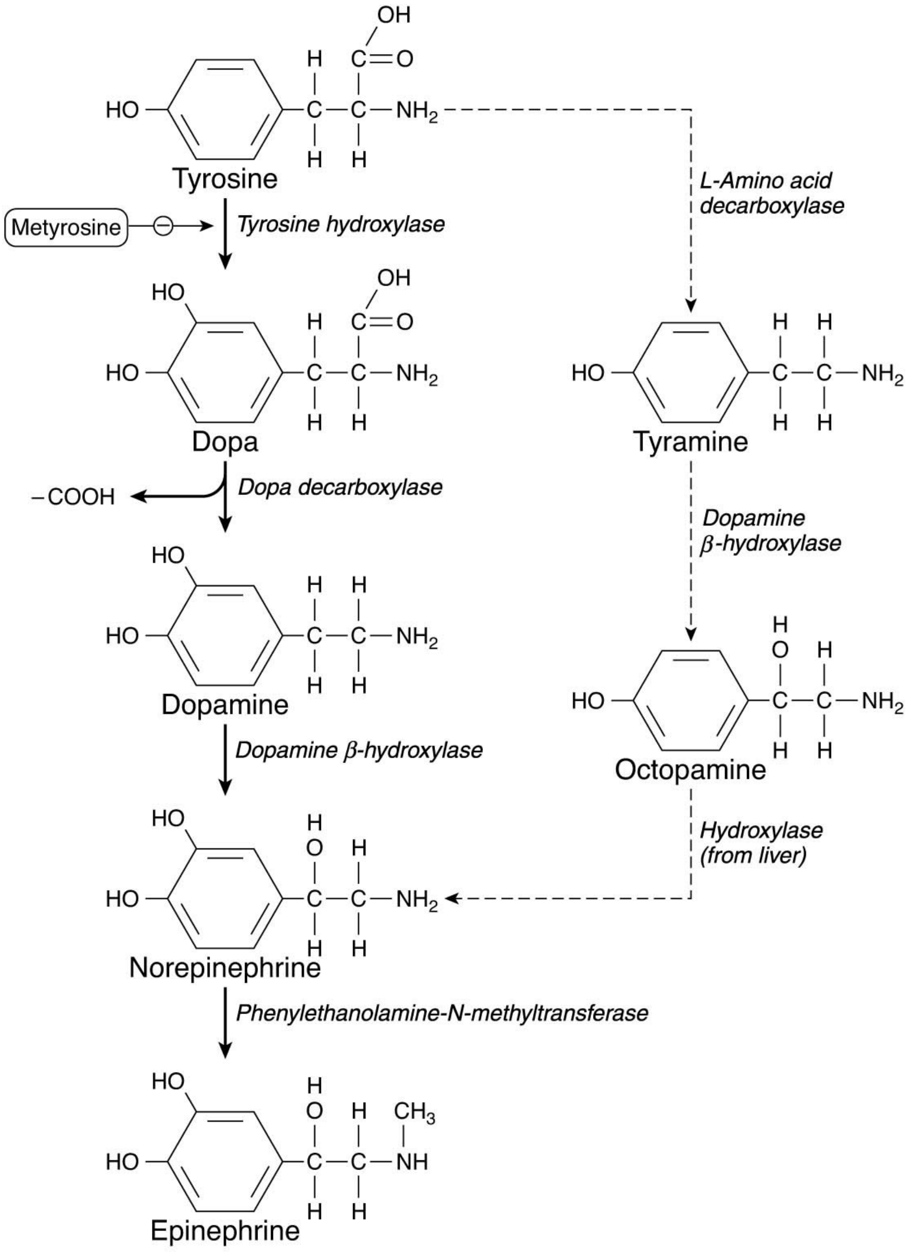

FIGURE 6–5 Biosynthesis of catecholamines. The rate-limiting step, conversion of tyrosine to dopa, can be inhibited by metyrosine (α-methyltyrosine). The alternative pathway shown by the dashed arrows has not been found to be of physiologic significance in humans. However, tyramine and octopamine may accumulate in patients treated with monoamine oxidase inhibitors. (Reproduced, with permission, from Greenspan FS, Gardner DG [editors]: *Basic and Clinical Endocrinology*, 7th ed. McGraw-Hill, 2003.)

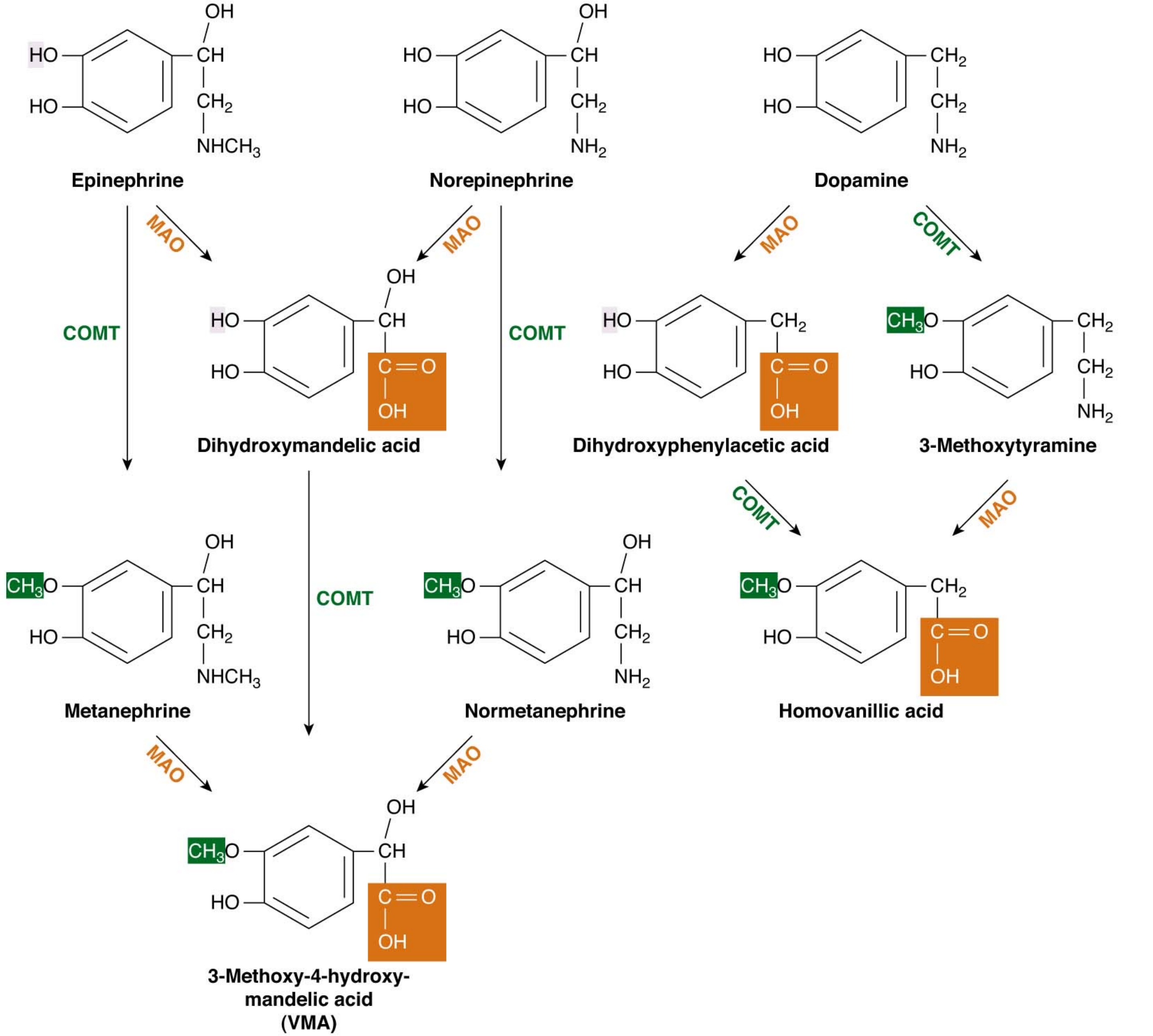

FIGURE 6–6 Metabolism of catecholamines by catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO). (Modified and reproduced, with permission, from Greenspan FS, Gardner DG [editors]: *Basic and Clinical Endocrinology*, 7th ed. McGraw-Hill, 2003.)

2. Norepinephrine

- 位於藍斑(locus caerulus) 或網狀系統的側頂蓋區(lateral tegmental area of the reticular formation)
- NE能去極化→potassium 傳導↑
- α_2 receptor是經由locus caerulus neurons
- 經由noradrenergic pathway→attention, arousal.

3. 5-HT

- 路徑起源於pons及upper brain stem之raphe或midline regions
- $5\text{-}HT_{1A}$和 $GABA_B$ →活化K^+ channel
- $5\text{-}HT_2$或$5\text{-}HT_5$ →blockade K^+ channel
- 經由serotonergic pathway →sleep, temperature, appetite, neuroendocrine control.

四、Peptides :

- Substance P: 與pain 有關
- Enkephalin, endorphin
- Somatosatin
- VIP (vasoactive intestinal polypeptide)

五、Nitric oxide

- CNS 有nitric oxide synthase (NOS)

→活化calcium –calmodulin

→活化NMDA(N-methyl-D-aspartate) receptor

→增加細胞內鈣離子濃度 → NO (血管平滑肌)

六、Endocannabinoids

- Cannabis (△9-tetrahydro cannabinol △9-THC)有特殊 Cannabinoid receptor (CB1) → psychoactive
- 與memory, cognition, pain有關。

TABLE 21–2 **Summary of neurotransmitter pharmacology in the central nervous system.**

Transmitter	Anatomy	Receptor Subtypes and Preferred Agonists	Receptor Antagonists	Mechanisms
Acetylcholine	Cell bodies at all levels; long and short connections	Muscarinic (M_1): muscarine	Pirenzepine, atropine	Excitatory: ↓ in K^+ conductance; ↑ IP_3, DAG
		Muscarinic (M_2): muscarine, bethanechol	Atropine, methoctramine	Inhibitory: ↑ K^+ conductance; ↓ cAMP
	Motoneuron-Renshaw cell synapse	Nicotinic: nicotine	Dihydro-β-erythroidine, α-bungarotoxin	Excitatory: ↑ cation conductance

TABLE 21–2 **Summary of neurotransmitter pharmacology in the central nervous system.**

Transmitter	Anatomy	Receptor Subtypes and Preferred Agonists	Receptor Antagonists	Mechanisms
Dopamine	Cell bodies at all levels; short, medium, and long connections	D_1	Phenothiazines	Inhibitory (?): ↑ cAMP
		D_2: bromocriptine	Phenothiazines, butyrophenones	Inhibitory (presynaptic): ↓ Ca^{2+}; Inhibitory (postsynaptic): ↑ in K^+ conductance, ↓ cAMP
GABA	Supraspinal and spinal interneurons involved in pre- and postsynaptic inhibition	$GABA_A$: muscimol	Bicuculline, picrotoxin	Inhibitory: ↑ Cl^- conductance
		$GABA_B$: baclofen	2-OH saclofen	Inhibitory (presynaptic): ↓ Ca^{2+} conductance; Inhibitory (postsynaptic): ↑ K^+ conductance

TABLE 21–2 Summary of neurotransmitter pharmacology in the central nervous system.

Transmitter	Anatomy	Receptor Subtypes and Preferred Agonists	Receptor Antagonists	Mechanisms
Glutamate	Relay neurons at all levels and some interneurons	*N*-Methyl-D-aspartate (NMDA): NMDA	2-Amino-5-phosphonovalerate, dizocilpine	Excitatory: ↑ cation conductance, particularly Ca^{2+}
		AMPA: AMPA	CNQX	Excitatory: ↑ cation conductance
		Kainate: kainic acid, domoic acid		
		Metabotropic: ACPD, quisqualate	MCPG	Inhibitory (presynaptic): ↓ Ca^{2+} conductance ↓ cAMP; Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
Glycine	Spinal interneurons and some brain stem interneurons	Taurine, β-alanine	Strychnine	Inhibitory: ↑ Cl^- conductance
5-Hydroxytryptamine (serotonin)	Cell bodies in midbrain and pons project to all levels	$5\text{-}HT_{1A}$: LSD	Metergoline, spiperone	Inhibitory: ↑ K^+ conductance, ↓ cAMP

TABLE 21–2 Summary of neurotransmitter pharmacology in the central nervous system. (Continued)

Transmitter	Anatomy	Receptor Subtypes and Preferred Agonists	Receptor Antagonists	Mechanisms
		$5\text{-}HT_{2A}$: LSD	Ketanserin	Excitatory: ↓ K^+ conductance, ↑IP_3, DAG
		$5\text{-}HT_3$: 2-methyl-5-HT	Ondansetron	Excitatory: ↑ cation conductance
		$5\text{-}HT_4$		Excitatory: ↓ K^+ conductance
Norepinephrine	Cell bodies in pons and brain stem project to all levels	α_1: phenylephrine	Prazosin	Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
		α_2: clonidine	Yohimbine	Inhibitory (presynaptic): ↓ Ca^{2+} conductance; Inhibitory: ↑ K^+ conductance, ↓ cAMP
		β_1: isoproterenol, dobutamine	Atenolol, practolol	Excitatory: ↓ K^+ conductance, ↑ cAMP

TABLE 21–2 Summary of neurotransmitter pharmacology in the central nervous system. (Continued)

Transmitter	Anatomy	Receptor Subtypes and Preferred Agonists	Receptor Antagonists	Mechanisms
Histamine	Cells in ventral posterior hypothalamus	H_1: 2(*m*-fluorophenyl)-histamine	Mepyramine	Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
		H_2: dimaprit	Ranitidine	Excitatory: ↓ K^+ conductance, ↑ cAMP
		H_3: *R*-α-methyl-histamine	Thioperamide	Inhibitory autoreceptors
Opioid peptides	Cell bodies at all levels; long and short connections	Mu: bendorphin	Naloxone	Inhibitory (presynaptic): ↓ Ca^{2+} conductance, ↓ cAMP
		Delta: enkephalin	Naloxone	Inhibitory (postsynaptic): ↑ K^+ conductance, ↓ cAMP
		Kappa: dynorphin	Naloxone	

TABLE 21–2 Summary of neurotransmitter pharmacology in the central nervous system. (Continued)

Transmitter	Anatomy	Receptor Subtypes and Preferred Agonists	Receptor Antagonists	Mechanisms
Tachykinins	Primary sensory neurons, cell bodies at all levels; long and short connections	NK1: Substance P methylester, aprepitant	Aprepitant	Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
		NK2		
		NK3		
Endocannabinoids	Widely distributed	CB1: Anandamide, 2-arachidonyglycerol	Rimonabant	Inhibitory (presynaptic): ↓ Ca^{2+} conductance, ↓ cAMP

Note: Many other central transmitters have been identified (see text).

ACPD, *trans*-1-amino-cyclopentyl-1,3-dicarboxylate; AMPA, DL-α-amino-3-hydroxy-5-methylisoxazole-4-propionate; cAMP, cyclic adenosine monophosphate; CQNX, 6-cyano-7-nitroquinoxaline-2,3-dione; DAG, diacylglycerol; IP_3, inositol trisphosphate; LSD, lysergic acid diethylamide; MCPG, α-methyl-4-carboxyphenylglycine.